

PREFACE

Although mitochondrial dysfunction is evident in intractable diseases such as Alzheimer's, Parkinson's, and mitochondrial diseases, there is a lack of therapeutic approaches that target the underlying pathogenic mechanisms. To identify rational therapeutic approaches, it is critical to clearly understand many aspects of mitochondrial biology in the brain, including normal and aberrant movement, turnover, metabolism, and the feasibility of genetic modification. Current interest in mitochondrial dynamics, bioenergetics, and metabolism in the brain has been greatly facilitated by rapidly evolving techniques allowing assessment of mitochondria within the context of intact cells and tissues. In no other cell type besides a neuron is the importance of mitochondrial trafficking and dynamic changes in morphology so readily apparent given the distances mitochondria must traverse between the cell body and a synapse. From a cell biology perspective, neurons must overcome unique challenges so that mitochondria can reach the nerve terminals and meet the energy demands of these electrically excitable cells.

Thus, this volume begins with a collection of excellent chapters addressing current techniques for the measurement of mitochondrial turnover, fusion and fission, and trafficking. Mitochondrial degradation through the autophagic pathway, a process termed mitophagy, is thought to be a quality control mechanism that is critical for maintaining a healthy population of mitochondria within cells. Chapters 1–3 detail methods to identify molecules involved in mitophagy and to measure the turnover of mitochondria. Mitochondrial fusion is a central aspect of mitochondrial dynamics, and Chapter 4 describes a method to directly quantify mitochondrial fusion in living, cultured cells. Mitochondrial transport is critical to the function of neurons, and multiple animal models have been developed to study this process. Chapters 5–9 detail methods to study mitochondrial transport in the neurons of mouse, fly, and zebrafish.

The second half of this volume addresses methods to assess mitochondrial function from diverse perspectives. As proteomic technologies have advanced, so has the need to identify the precise localization of newly discovered mitochondrial proteins, and a technique to do so is addressed in Chapter 10. The juxtaposition of mitochondrial outer membranes with specialized areas of the endoplasmic reticulum is a topic of interest to those studying signaling events and lipid homeostasis, and thus methods for the

study of mitochondria-associated membranes are addressed in Chapter 11. The importance of mitochondrial reactive oxygen species production and iron metabolism to normal cell function and disease pathogenesis continues to be a topic of interest, yet remains challenging to assess, which is a topic of Chapters 12–15. The advent of plate-based technologies for the measurement of cellular bioenergetic function has revolutionized the rate of acquisition and scope of data detailing how cells meet their energy requirements. Expert guidance for interpretation of plate-based respirometry and extracellular acidification data is provided in Chapter 16. Chapter 17 details an exciting fluorescence imaging approach to providing real-time measurement of the ATP/ADP ratio. The discovery of treatments for mitochondrial diseases requires improved methods for modeling the defects in patients' cells which is addressed in Chapter 19, and Chapter 18 describes an exciting approach for engineering a mitochondrial targeted endonuclease to rectify defects in mitochondrial DNA. Both chapters hold promise for the design of future therapeutic intervention for these devastating diseases. The final two chapters (Chapters 20 and 21) address assessment of mitochondrial function *in vivo* using PET and MRI approaches, representing technologies that may become not only important diagnostic tools but also the means to monitor the efficacy of potential therapeutic responses. We hope these chapters will provide a resource and practical guidelines for those interested in further characterization of normal and dysregulated mitochondrial function and lead to new insights into the pathogenic mechanisms operating in neurodegenerative disorders.

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